REMARKS

This is responsive to the office action dated January 6, 2010. By this Response, Claims 48, 54-56, 62, 75, 93, 100 and 105 are amended, Claim 49-53, 73 and 79 are canceled, New Claims 110-117 are added, and Claims 48, 54-64, 75-77, 93, 100, 103-106, and 110-117 are pending for examination. It is submitted that the rejections are overcome in view of the amendments and/or remarks presented herein, and that the application is in condition for allowance. Favorable reconsideration of the application is respectfully requested.

REJECTIONS UNDER 35 U.S.C. §102

The Office Action rejected claims 48 and 49 under 35 U.S.C. §102(a) and (e) as being anticipated by Reff et al. (WO 03/006607, IDS). Claim 48 is rejected under 35 U.S.C. §102(b) as being anticipated by Rao et al. (PNAS, 1992, Vol. 89, pages 7742-7746).

Claim 48 has been amended to recite:

> wherein the third cistron and the fourth cistron are contained in a retroviral vector, wherein the third cistron and fourth cistron are associated with a ubiquitous chromatin opening element (UCOE), an insulator, or a barrier element, and wherein the third cistron and the fourth cistron are separated by an internal ribosome entry site (IRES) . . . .

These limitations and the arrangement of these limitations as claimed is not disclosed in Reff or Rao, and thus, this rejection is obviated by the amendments to claim 48. *See Linear Technology Corp. v. International Trade Commission*, 566 F.3d 1049 (Fed. Cir. 2010) (*citing Net MoneyIn, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1370 (Fed. Cir. 2008) ("[A]n anticipatory reference [must] show all of the limitations of the claims arranged or combined in the same way as recited in the claims")

REJECTIONS UNDER 35 U.S.C. §103

Claims 50-52, 56, 58-64 and 103 are rejected under 35 U.S.C. §103(a) as being unpatentable over Reff et al. (IDS), in view of Cockett et al. (IDS) and Rao et al. (PNAS, 1992. Vol. 89, pages 7742-7746). Claims 53-55, 57, 73, 75-77, 79, 93, 100, 104-106 are rejected under 35 U.S.C. §103(a) as being unpatentable over Reff, Cockett and Rao et al., as applied to claims

50-52, 56, 58-64 and 103 above, and further in view of Antoniou et al. (WO 00/05393, see IDS). The Applicants respectfully traverse these rejections because the cited prior art (1) fails to teach all the limitations of the now amended claims, and (2) fails to provide a reasonable expectation of success.

Claims 50-53 have been canceled. Claims 54 and 55 depend from amended claim 48 that now recites:

> wherein the third cistron and the fourth cistron are contained in a retroviral vector, wherein the third cistron and fourth cistron are associated with a ubiquitous chromatin opening element (UCOE), an insulator, or a barrier element, and wherein the third cistron and the fourth cistron are separated by an internal ribosome entry site (IRES) . . . .

Reff, Cockett and Rao et al. do not teach these limitations of the amended claims.

Independent Claims 56, 62, 93, and 100 have been amended to recite new limitations that require the transactivator be expressed at a level that can cause cell death, and that the apoptosis-protective protein be expressed at levels to inhibit cell death caused by the transactivator. In addition, New Claims 110-117 add limitations to these independent claims that require an increase in productivity of 2-5 fold from the transactivator and apoptosis-protective protein. These new limitations are not disclosed in Reff, Cockett, Rao or Antoniou, and it would not be obvious to add these limitations to Reff, Cockett, Rao or Antoniou.

Reff teaches that apoptosis will naturally occur in the life cycle of a host cell recombinantly expressing a desired polypeptide, when that host cell is exposed to external factors such as nutrient limitation (*e.g.*, serum deprivation), toxic agents in the growth media (e.g., waste products from cell growth), or physical stresses. Reff demonstrates enhanced host cell performance when host cell life is extended beyond these limiting factors through the use of an apoptosis protective protein that prevents or delays apoptosis caused by these factors. (See Reff at ¶¶ 9, 98-99, 100-102.) In view of the objects of the Reff invention, it would be detrimental to the host cell to add a factor that would artificially increase apoptosis, such as the claimed levels of a transactivator. Reff also provides no insights as to the reasonably expected

results from this combination as recited in Claims 110-117. Thus, it would not be obvious to obviate the objects of the Reff reference by combining it with toxic levels of transactivator protein as recited in the amended claims.

The pending claims are nonobvious because the Reff publication extols the benefits of reducing natural apoptosis in a recombinant host cell to enhance host cell performance, and adding to the host cells a transactivator that would artificially induce apoptosis would interfere with and be detrimental to the object of the Reff publication. *See Eisai Co. Ltd. v. Dr. Reddy's Lab., Ltd*, 87 USPQ2d 1452, 1456 (Fed. Cir. 2008) ("The record, however, shows no discernible reason for a skilled artisan to begin with lansoprazole only to drop the very feature, the fluorinated substituent, that gave this advantageous property.") *I.e.*, the object of the Reff publication is to reduce natural apoptosis and it would antithetical to that goal to artificially introduce to the host cell factors that would increase apoptosis over the natural factors.

As acknowledged in the Office Action, Cockett teaches that high levels of transactivator in a host cell inhibited cell growth and so degraded host cell performance. (See abstract.) But, when low levels of transactivator were expressed in the host cell, cell growth did not stop and the transactivator induced expression of a desired polypeptide in the host cell. (*Id.*) Thus, Reff combined with Cockett would teach that the host cells of Reff should be combined with low (non-toxic) levels of a transactivator. It would not be obvious from Cockett to modify Reff with toxic levels of a transactivator. Cockett also provides no insight regarding the reasonably expected result from the combination of this toxic level of transactivator combined with an apoptosis protective protein. Thus, Reff and Cockett do not provide a reasonable expectation of success.

Rao teaches that the non transformed cells in primary cultures of rat kidney cells can be converted to a transformed cell type (tumor cell) by E1A protein, but after an initial burst of growth many cells die (by an apoptosis like process), and immortalized clones will arise from these E1A primary cells after 5-6 weeks. (See abstract, p. 7743, first col., first full paragraph.) Rao also teaches that the E1B protein can prevent the death of many of the E1A expressing cells

after the initial burst of cell growth. (*Id.*) Host cell lines of the claimed invention are already immortalized (transformed), and the Rao results with primary cell cultures are not predictive of the immortalized host cells of the claimed invention. Also, Rao was studying transformation of cells, and not recombinant protein expression by an already transformed host cell, and so, Rao fails to provide a reasonable expectation of success for the claimed invention as well. Thus, a person of skill in the art would not have a reason to combine Rao with Reff and Cockett, and assuming arguendo that a person of skill in the art would combine Rao with Reff and Cockett there would be no reasonable expectation of success, *i.e.*, that expression of a transactivator with an apoptosis-protective protein would increase recombinant protein levels in the host cell culture.

Antoniou was cited for teaching UCOE and IRES elements in an expression vector. These teachings do not bridge the gaps in Reff, Cockett and Rao, regarding the invention of the amended claims.

The facts around Reff, Cockett, Rao and Antoniou are similar to those in the 2010 Federal Circuit decision, *Kinetic Concepts*. *See Kinetic Concepts, Inc. v. Blue Sky Med. Grp, Inc.*, 554 F.3d 1010 (Fed. Cir. 2010); *see also, Honeywell Int'l, Inc. v. U.S.*, 93 USPQ2d 1740, 1747 (Fed. Cir. 2010) (prior art failed to teach perceptible red light as required by the claim). In *Kinetic Concepts*, none of the asserted prior art taught "treating a wound with negative pressure" and so the Federal Circuit affirmed the District Court's holding of nonobviousness. *Id.* Similarly, the amended claims are patentable over Reff, Cockett, Rao and Antoniou because these references do not teach recombinant expression in a host cell (an immortalized cell) using levels of transactivator that would be toxic in the absence of an apoptosis-protective protein to increase the production of the desired protein.

For all the above reasons, Applicant respectfully submits that the amendments to the claims overcome the obviousness rejections combining Reff with Cockett, Rao and Antoniou.

CONCLUSION

Applicants believe that this application is in condition for allowance, and request that the Examiner give the application favorable reconsideration and permit it to issue as a patent. If the Examiner believes that the application can be put in even better condition for allowance, the Examiner is invited to contact Applicant's representatives listed below.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 500417 and please credit any excess fees to such deposit account.

Respectfully submitted,

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